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Screening for Oral Cancer: A Targeted Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objectives: To assess whether screening for oral cancer reduces morbidity or mortality and to determine the performance characteristics of the oral screening examination for cancer or potentially malignant disorders (PMDs).

Data sources: Building on previous searches, we searched Medline from January 2008 through July 2011. We supplemented searches with bibliographies from retrieved articles and from previous U.S. Preventive Services Task Force (USPSTF) reviews.

Methods: One investigator reviewed citations at the title and abstract level; two investigators independently reviewed potentially relevant citations at the full-text level using predefined inclusion and exclusion criteria. A single investigator extracted study characteristics and results; a second investigator confirmed data. Two investigators rated the studies for internal validity using USPSTF criteria. Evidence was described in text and tables and summarized by qualitative analysis.

Results: Evidence for the effect of oral screening on morbidity and mortality came from a single, large randomized, controlled trial (n=191,873) conducted in a population with high disease prevalence using home-based screening by advanced health workers. Screened subjects had no significant difference in incidence or mortality rates from oral cancer compared with subjects who were not screened. However, screened subjects had oral cancer diagnosed at lower stages and with greater 5-year survival. Within the subgroup who used tobacco or alcohol (n=84,600), screened subjects had a lower mortality rate from oral cancer than subjects who were not screened. Evidence for the performance characteristics of the screening examination came from seven primary studies (n=49,120), most conducted in settings with much higher incidence and mortality from oral cancer than the United States. Studies also had considerable heterogeneity in design and showed wide variation in performance characteristics. Screening examinations by general dentists in the United Kingdom among 2,336 presumably higher-risk patients age 40 years and older showed sensitivity for oral cancer or PMD of 71 to 74 percent, with positive predictive value of 67 to 86 percent and specificity of 98 to 99 percent. Adding toluidine blue dye to a screening examination did not significantly change its performance, as measured by the malignant transformation rate or incidence of oral cancer.

Conclusions: We found no evidence on screening either a general or a selected high-risk population for oral cancer in the United States. Screening subjects in a high-prevalence population outside the United States lowered the stage of oral cancer at diagnosis and improved 5-year survival. However, survival differences could represent length or lead-time bias. Screening subjects in the subgroup who used tobacco or alcohol reduced the mortality rate from oral cancer. Subgroup analyses, however, were post-hoc and should be viewed as exploratory. The performance characteristics of the screening examination varied widely, with applicable results only from dentists addressing higher-risk patients in the United Kingdom. However, sensitivity and specificity estimates were for PMDs as well as cancers, and do not represent a clear screening strategy that is applicable to U.S. practice. We found no evidence that any adjunctive device affects the performance of the screening examination.

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CHAPTER 1. INTRODUCTION

Background

In 2004, the U.S Preventive Services Task Force (USPSTF) found insufficient evidence in its review[1] to recommend for or against screening for oral cancer.[2] In this review, we are updating the evidence search and analysis to allow this recommendation to be reconsidered.

Disease Condition

Oral cancer includes cancers of the lip, oral cavity, and pharynx.[3] Ninety percent of cancers of the oral cavity are squamous cell carcinomas (SCCs) arising from the mucosal lining. The other 10 percent of oral cancers are malignant melanomas, salivary gland tumors, sarcomas of the soft tissues or jaw bones, nonHodgkin's lymphomas, or metastases from extra-oral primary tumors.[4]

Etiology and Natural History

Most oral cancer is preceded by visible nonmalignant lesions.[5] Since not all nonmalignant lesions progress to cancer, the World Health Organization recommends classifying them as "potentially malignant disorders" (PMDs), rather than "precancers," "precursor lesions," or "premalignant lesions."[6] PMDs are oral lesions that include leukoplakia, erythroplakia, lesions of the palate from reverse smoking (placing the lighted end of a cigarette in the mouth), submucous fibrosis, and actinic keratosis (with potential for lip cancer). Whether lichen planus and discoid lupus erythematosus are potentially malignant is controversial. There are also rare hereditary diseases (e.g., dyskeratosis congenita and epidermolysis bullosa) that involve PMDs.[6]

Most PMDs are oral leukoplakia or erythroplakia.[7] An estimated 2.6 percent of the world's population has oral leukoplakia.[8] While the reported malignant transformation rate varies widely,[9] a pooled estimate is 1.36 percent per year.[8] An estimated 0.2 to 0.8 percent worldwide has erythroplakia,[7] which has a malignant transformation rate above 85 percent.[10]

Prevalence and Burden of Disease

According to data from the American Cancer Society, an estimated 39,400 new cases of cancer of the oral cavity and pharynx were expected in 2011, leading to an estimated 7,900 deaths.[11] Based on 2004 to 2008 Surveillance Epidemiology and End Results (SEER) data, the overall age-adjusted incidence rate of oral cancer in the United States was 10.6 per 100,000 individuals and the median age at diagnosis was 62 years.[12] Incidence rates begin to increase at approximately ages 35 to 44 years (**Figure 1**).[13,14] Men had higher incidence rates for oral cancer than women in all racial and ethnic groups. In the past, black men and women had higher incidence rates than white men and women,[7,10,15] but recent data show white men and women (Hispanic and nonHispanic) having higher incidence rates than black men and women.[12]

Based on 2004 to 2008 SEER data, the age-adjusted mortality rate was 2.5 per 100,000 individuals per year and the median age of death from oral cancer was 67 years.[12] Men had higher mortality rates for oral cancer than women and black men, specifically, had the highest mortality rates. The mortality rate for oral cancer has been decreasing in the United States since 1975.

Based on 2001 to 2007 SEER data, the relative 5-year survival for all those diagnosed with oral cancer was 60.8 percent compared with the general population.[12] Relative 5-year survival decreased with more advanced cancer stage at diagnosis, from 82.4 percent for localized disease, to 55.5 percent for regional lymph node spread, to 33.2 percent for disease with distant metastases.[12] The lifetime risk for oral cancer was 1.02 percent, meaning one in 98 men and women will be diagnosed with oral cancer during his or her lifetime.[12]

Risk Factors

Several lifestyle factors, particularly tobacco use, affect an individual's risk of acquiring oral cancer. Worldwide, 20 to 30 percent of oral cancer cases are attributable to cigarette smoking.[16] A pooled analysis of 15 studies estimated the effects of smoking cigarettes among people who never drank alcohol.[17] Compared with never-smokers, all smokers combined had an adjusted odds ratio (OR) of 1.35 (95% confidence interval [CI], 0.90 to 2.01) for cancer of the oral cavity. The adjusted OR showed a dose-response relationship with smoking intensity and duration. Compared with never-smokers, smokers of 31 to 40 cigarettes (1.5 to 2 packs) per day had an adjusted OR of oral cancer of 2.92 (95% CI, 0.91 to 9.44), with an increased adjusted OR of 3.23 (95% CI, 1.54 to 6.77) in those who smoked more than 40 years. Thus, while all levels of cigarette smoking increase risk of oral cancer at a population level, relatively heavy or long-term use is required to identify individuals or subgroups with substantial risk. The same pooled analysis estimated the effects of drinking alcohol among people who never smoked.[17] Those who ever drank alcohol had an adjusted OR of 1.17 (95% CI, 0.92 to 1.48) for cancer of the oral cavity compared with never-drinkers. The adjusted ORs did not show a dose-response relationship.

An earlier case-control study that adjusted for smoking status (as well as other factors), however, found increasing adjusted ORs for oral or pharyngeal cancer with increasing frequency of alcohol consumption: up to 8.8 (95% CI, 5.4 to 14.3) for men and 9.1 (95% CI, 3.9 to 21.0) for women who had 30 or more alcoholic drinks per week compared with men and women who had less than one alcoholic drink per week.[18] This study also examined possible synergistic effects of smoking and drinking alcohol. The adjusted OR for oropharyngeal cancer increased to 37.7 for men who both smoked 40 or more (two packs) cigarettes a day for 20 or more years and had 30 or more alcoholic drinks per week.[18] Thus, relatively heavy alcohol use (50% to 100% above recommended levels for moderate drinking) convey increased risk of oral or pharyngeal cancer, which is exponentially increased further in heavy, long-term male smokers.

Whether age itself is a risk factor for oral cancer or is simply a marker for longer exposure to other risk factors remains unclear. In the pooled analysis of 15 studies, analyses for smoking risks among never-drinkers were stratified by age, race, ethnicity, education level, and study design. These analyses found no strong differences between the strata. Similarly, analyses for risks of drinking alcohol among those who never smoked were stratified by age, sex, race/ethnicity, education level, study region, and source of control subjects. Again, no differences between strata were found.[17]

Southeast and south Asia have some of the highest incidence and mortality rates from oral cancer in the world.[19] This is attributed to smoking tobacco, reverse smoking, and chewing betel quid.[7,16] Betel quid contains areca nut, lime, flavorings, and tobacco wrapped in betel leaves. It is chewed by 25 to 50 percent of the populations of southeast and south Asia.[16]

Human papillomavirus (HPV) is also associated with oral SCC and PMDs.[20] The tonsil, oropharynx, and the base of the tongue are specific oral SCC sites with a high prevalence of HPV.[21] In a pooled analysis of 39 studies, HPV was significantly more likely to be detected in tissue samples from patients with oral SCC (OR, 3.98 [95% CI, 2.62 to 6.02]) or PMDs (OR, 3.87 [95% CI, 2.87 to 5.21]) compared with similar samples from control subjects.[22] Globally, the prevalence of HPV in oral SCC is 23.5 percent.[23] Patients with HPV-positive oral cancer are diagnosed an average of 5 years younger and have improved survival compared with patients with HPV-negative oral cancer.[21,24] The role of the Epstein-Barr virus in oral cancer is currently being investigated.[24,25]

Exposure to ultraviolet light also increases an individual's risk of lip cancer.[15] Other risk factors for oral cancer include infection with *Candida* or bacterial flora and a compromised immune system.[10]

The presence of infectious and environmental risk factors for oral cancer suggests multiple pathways for its pathogenesis. While some oral cancers originate through tobacco and alcohol use, others originate through oral HPV infection and associated sexual behavior.[21,26] The overall decrease in the incidence rate of oral cancer in the United States since 1979[12] is attributed to declines in cigarette smoking and alcohol consumption.[21] While blacks used to have higher incidence rates of oral cancer than whites, whites now have higher incidence rates than blacks. This change is attributed to increases in oral cancer related to HPV infection among whites (particularly in younger age cohorts), along with decreases in both HPV-related and HPV-unrelated oral cancers among blacks.[21] The prevalence of oral HPV infection is associated with age, sex, life-time number of sexual partners, and number of cigarettes smoked per day.[26]

Current Clinical Practice

According to the World Health Organization and the National Institute of Dental and Craniofacial Research, an oral cancer screening examination should include a visual inspection of the face, neck, lips, labial mucosa, buccal mucosa, gingiva, floor of the mouth, tongue, and palate. Mouth mirrors can help visualize all surfaces. This examination should also include palpating the regional lymph nodes, tongue, and floor of the mouth. Any abnormality that lasts for more than 2 weeks should be re-evaluated and considered for biopsy.[27]

Several adjunctive devices have been developed to aid in screening. Toluidine blue (also known as tolonium chloride) is a dye that stains rapidly dividing cells, helping to visually identify abnormal tissue. Chemiluminescent and autofluorescent lighting devices are also used to help visualize abnormal tissue based on the premise that abnormal tissue has different absorptive and reflective characteristics than normal tissue. In brush cytopathology, a clinician uses a brush to obtain a full-thickness sample of cells from a suspicious lesion. The cells are then fixed on a slide, stained, and analyzed under a microscope to determine whether the lesion is potentially malignant.[28,29]

In a 2008 survey of adults in the United States, 29.4 percent reported ever having an oral cancer screening examination that involved pulling on their tongue or feeling their neck.[30] Increasing the proportion of oral cancers detected at the earliest stage by 10 percent is an objective of Healthy People 2020, by increasing the proportion of adults who have received an oral cancer screening examination from a dentist or dental hygienist during the previous year.[31]

Previous USPSTF Recommendation

In 2004,[2] the USPSTF reviewed available data and concluded there was insufficient evidence to recommend for or against routine screening for oral cancer in adults. The recommendation was based on early[32] and interim[33] reports of a cluster-randomized, controlled trial of screening by health care workers in India, which found no differences in mortality rates from oral cancer between the screened and control groups. Our review found eight randomized, controlled trials (RCTs) using various treatments for oral leukoplakia that showed treatment promotes remission. These studies were small, however, and had less than 2 years of followup.

Scope and Purpose

The USPSTF requested this targeted update to focus on the evidence gap in the conceptual framework about screening for oral cancer (i.e., any test or combination of tests used to detect PMDs or cancer of the lip, oral cavity, or pharynx). The two key questions are:

Key Question 1 (KQ 1): Does screening for oral cancer reduce morbidity or mortality?

Key Question 2 (KQ 2): What are the performance characteristics of the screening oral examination as a means of identifying oral cancer or PMDs for oral cancer?

CHAPTER 2. METHODS

Data Sources and Searches

We searched Ovid Medline for English-language articles published between January 2008 and July 11, 2011. Previous interim searches conducted for the USPSTF covered 1994 through October 6, 2008. The relevant studies they identified are included here. Our current search strategy used MeSH terms and key word variations in the title or abstract to identify citations related to oral cancer, screening, and diagnostic accuracy (**Appendix A**).

Study Selection

One investigator reviewed the citations retrieved at the title and abstract level, identifying possibly relevant articles. Two investigators independently reviewed citations identified at the full-text level. Disagreements were resolved by discussion and consultation with a third reviewer.

For KQ 1, studies were included if they were RCTs, meta-analyses, or systematic reviews that compared a screening test or combination of tests with no screening or usual care in adult populations (at least 80% of subjects were age 18 years or older) and reported morbidity or mortality outcomes. For KQ 2, studies were included if they compared a uniformly applied screening test for oral cancer with a reference standard (second examination, other test, or longitudinal followup) that was applied to all persons with positive screens and at least a sample of persons with negative screens. Relevant studies identified by previous USPSTF searches were carried forward to our review. Finally, we examined bibliographies of the articles retrieved for additional relevant studies.

Data Extraction and Quality Assessment

A single investigator extracted study characteristics and results. A second investigator confirmed data. Two investigators rated the studies for internal validity using USPSTF criteria supplemented by standards from established criteria for assessing systematic reviews, RCTs, or diagnostic accuracy.[34-36] Per USPSTF methods, articles that were rated as having poor quality were excluded from further consideration.

Data Synthesis and Analysis

We describe the evidence in text and tables by KQ and summarize it qualitatively. We did not synthesize the data quantitatively, since there was scant evidence for KQ 1 and the evidence for KQ 2 was too heterogeneous to pool. For KQ 2, we report sensitivity, specificity, positive predictive value, and negative predictive value where possible.

Role of the Funding Source

This research was partially conducted by the Agency for Healthcare Research and Quality (AHRQ) and then updated and finalized under contract to support the work of the USPSTF. AHRQ staff provided oversight and reviewed the draft synthesis.

CHAPTER 3. RESULTS

Literature Search

Our literature search retrieved 1,722 citations and we selected 89 of these for full-text review. In addition, we reviewed nine studies identified in previous USPSTF searches.[32,33,37-43] After our full-text review, we excluded 88 studies (**Appendix B**). Three articles pertaining to KQ 1 report the same trial after each of the three rounds of screening.[32,33,37] Seven articles pertaining to KQ 2 report test performance characteristics of different screening modalities.[38-41,44-46]

Key Question 1. Does Screening for Oral Cancer Reduce Morbidity or Mortality?

Summary of Results

Evidence for this KQ is derived from a single large, fair-quality RCT conducted in India—the Trivandrum Oral Cancer Screening Study.[37] Screened subjects had oral cancer diagnosed at lower stages with greater 5-year survival than patients who were not screened. Within the subgroup of participants who used tobacco or alcohol, screened subjects had a significantly lower mortality rate from oral cancer than subjects in the control group. We found no evidence on screening for oral cancer in either the general U.S. population or a selected high-risk U.S. population.

Study Details

This RCT was conducted in the Trivandrum District in the state of Kerala, India, an area with the fourth highest incidence rate of oral cancer in the world (16.3 per 100,000 men and 7.7 per 100,000 women during 1991 to 1992) due to the prevalence of chewing betel quid and smoking tobacco.[32] In this cluster-randomized design, 13 administrative districts were assigned to a screening intervention for their residents or to serve as controls. In the seven districts assigned to screening, advanced health workers conducted a visual inspection and palpation during home visits. The health workers referred residents with abnormal lesions to a specialty clinic. Screening was repeated every 3 years for at most three rounds. The diagnostic accuracy of this screening examination was reported in a companion study[40] and is described under KQ 2. In control districts, health workers provided routine care and health messages, advising those subjects who used alcohol or tobacco to stop doing so.

In total, there were 191,873 eligible subjects throughout the study period, as more residents became eligible with each round: 59,894 residents in screened districts and 54,707 in control districts after the first round, 78,969 in screened districts and 74,739 in control districts after the second round, and 96,517 in the screened districts and 95,356 in the control districts after the third round. In the first two rounds, more eligible residents in the screened districts smoked tobacco, chewed tobacco (mainly as betel quid), or drank alcohol than in the control districts.

The prevalence of these risk factors became more balanced by the third round, with no significant differences between screened and control districts in the proportions of eligible men or women who chewed tobacco or drank alcohol. Despite this, smoking remained more prevalent in the screened districts: 63 percent of men in screened districts smoked, whereas 56 percent in control districts smoked (p=0.0455); 3 percent of women in screened districts smoked, whereas 1 percent in control districts smoked (p=0.0633). In the screened districts, 87,655 (91% of those eligible) were screened at least once over the three rounds of screening: 34,343 (36%) were screened once, 24,210 (25%) were screened twice, and 29,102 (30%) were screened three times.

Clinical outcomes included oral cancer incidence, stage at diagnosis, survival, and deaths due to oral cancer. These outcomes were ascertained from cancer registries, hospital records, pathology laboratories, and death records. Outcomes were calculated using intention-to-screen analyses. After the third round, 5,145 residents had oral lesions on the screening examination. Of these residents, 3,218 (63%) received followup care at the specialty clinic, where 2,383 were confirmed to have a potentially malignant lesion or oral cancer. The cumulative incidence rate of oral cancer during the 9 years after screening began did not differ significantly between the screened and control districts: 43.7 per 100,000 person-years in the screened districts versus 37.6 per 100,000 person-years in the control districts (rate ratio [RR], 1.16 [95% CI, 0.70 to 1.92]). The oral cancers within the screened districts were at lower stages when diagnosed than within the control districts: 25 percent in the screened district versus 13 percent in the control districts were at stage I; 17 versus 11 percent were at stage II; 18 versus 22 percent were at stage III; and 33 versus 44 percent were at stage IV, respectively. The screened districts had a significantly greater proportion of stage I or stage II oral cancer cases (41%) compared with the control districts (23%; p=0.004). Residents with oral cancer from the screened districts had a 50 percent 5-year survival rate, while those from control districts had only a 34 percent 5-year survival rate (p=0.009). The overall mortality rate from oral cancer, however, did not differ significantly between the two groups: 16.4 per 100,000 person-years in the screened districts versus 20.7 per 100,000 person-years in the control districts (RR, 0.79 [95% CI, 0.51 to 1.22]).

Study investigators also stratified their analyses by subjects' tobacco or alcohol use. Among the 84,600 eligible subjects who used tobacco or alcohol (44% of the total), subjects in the screened districts had no significant difference in incidence of oral cancer (81.1 per 100,000 in the screened districts vs. 83.3 per 100,000 in the control districts; RR, 0.97 [95% CI, 0.66 to 1.44]), but significantly lower mortality from oral cancer than subjects in the control districts (29.9 per 100,000 in the screened districts vs. 45.4 per 100,000 in the control districts; RR, 0.66 [95% CI, 0.45 to 0.95]). Among subjects who did not use tobacco or alcohol, there were no significant differences in incidence or mortality from oral cancer between screened and control districts. The authors concluded that oral cancer screening conducted by trained health workers reduced oral cancer mortality in people who were at high risk due to using tobacco or alcohol.

This study was rated fair quality despite its randomized design, specific eligibility requirements, large sample size, validated screening test, ascertainment of outcomes equally for both groups, use of objective outcomes, and intention-to-treat analysis. Limitations detailed in other systematic reviews[5,29] include imbalance in baseline risk factors, inadequate accounting for clustering in the analysis, low compliance with followup, possible lead-time and length-time bias, reporting outcomes cumulatively (rather than for each round of screening), and not reporting adverse effects of screening or how lesions were treated. The higher prevalence of risk factors in the screened group may have diluted the apparent effectiveness of screening. This imbalance was addressed somewhat by the subgroup analyses according to tobacco or alcohol use, although the analyses were not prespecified. A better approach would have been examining effect modification by tobacco or alcohol use with tests for interaction.[47,48] Finally, despite its large size, the study was underpowered. In the sample size calculations, each district was assumed to accumulate 110,000 person-years of observation over the 9 years. The seven districts randomized to screening, however, accumulated only 469,089 person-years of observation, while the six control districts accumulated only 419,748 person-years of observation.

Key Question 2. What Are the Performance Characteristics of the Screening Oral Examination as a Means of Identifying Oral Cancer or Potentially Malignant Disorders for Oral Cancer?

Summary of Results

Evidence from seven fair- to good-quality primary studies[38-41,44-46] showed considerable heterogeneity in design and wide variation in performance characteristics (**Table 1**). Most were conducted in settings (Taiwan, India) with much higher incidence and mortality from lip and oral cancer than the United States. Across all studies, sensitivity for oral cancer or PMD ranged from 18 to 94.3 percent, and specificity from 54 to 99.9 percent. The positive predictive value ranged from 17 to 86.6 percent and the negative predictive value from 73 to 99.3 percent. In two studies of screening by general dentists in the United Kingdom,[38,39] which is more comparable to the United States in oral cancer incidence and mortality, one good-quality study among 2,027 relatively high-risk dental patients age 40 years and older found that dental examination showed a sensitivity of 74 percent and a specificity of 99 percent, with a positive predictive value of 67 percent.[39] Another fair-quality study among a mixed sample of 292 workers with unknown smoking or alcohol use habits found a similar sensitivity (71%), specificity (99%), and positive predictive value (86%).[38] These results reflect detection of PMDs as well as oral cancers, reflect an imperfect reference standard (more expert examination), and thus need to be confirmed with longitudinal followup. One fair- to poor-quality, very small trial of self-examination in patients age 45 years and older in the United Kingdom found very low sensitivity, specificity, and predictive values.[45] The only study that evaluated an adjunctive screening method in Taiwan found no improvement in clinical outcomes when toluidine blue gargle preceded the dental oral examination.[46] None of the studies reported on harms from the screening test or from false-positive or false-negative test results. No studies evaluating other adjuncts (chemiluminescent lighting, autofluorescent lighting, or brush cytopathology) met our inclusion criteria.

Study Details

Screening by health workers. Two studies conducted in the Trivandrum District in Kerala, India assessed screening examinations by health workers.[40,41] One fair-quality study assessed screening by basic health workers who had a high school diploma, a 1-year certification course, and an additional 2 or 5 days of training about oral cancer screening.[41] The basic health workers made home visits, screening residents who were age 35 years or older and used tobacco—an estimated 25 percent of the population. The health workers advised subjects who had a lesion that was suspicious for a potentially malignant or malignant disorder to follow up at an oral cancer detection center. They advised subjects who had a lesion that was not suspicious for malignancy to stop using tobacco and have periodic re-examinations. The basic health workers screened 39,331 subjects, referring 523 (1.3%) to the oral cancer detection center. Of those referred, 351 (67%) reported to the referral center. A sample of 1,921 (5%) screened subjects were re-examined by a dentist after 6 months to assess the basic health worker's screening examination. Screened subjects—some of whom had a referable lesion on the screening examination—were selected for re-examination if they lived near someone with a referable lesion. Using the dentist's examination as a reference standard, the screening examination by the basic health worker showed a sensitivity of 59 percent, specificity of 98 percent, positive predictive value of 31 percent, and negative predictive value of 99 percent. This study was rated as fair quality because of low adherence with referral by screen-positive subjects, because of the delay between screening test and reference standard administration, and because it did not report whether subjects with known oral lesions were excluded or whether dentists were aware of the results of the basic health worker's examination.

A good-quality study[40] was conducted as part of the RCT described under KQ 1[37] after the RCT had recruited 9,000 subjects over a 5-month period. As part of the RCT, screening was performed by advanced health workers who were university graduates with 6 weeks of special training. Screening examinations took place in subjects' homes using visual inspection and palpation. Subjects were eligible for screening if they were ages 35 to 64 years and lived in a district randomized to screening. A subset of 2,069 (23% of those screened as part of the RCT) subjects were re-examined to assess the advanced health workers' screening examination. Subjects were re-examined if they lived in densely populated areas, whether they had screened positive or negative. The re-examination was conducted in the subjects' homes by the original screening health care worker and one of three physicians 1 to 6 months after the screening examination. Using the physicians' examination as the reference standard, the advanced health workers' repeat examination showed a sensitivity of 94.3 percent, specificity of 98.3 percent, positive predictive value of 86.6 percent, and negative predictive value of 99.3 percent. Although the proportion using tobacco or alcohol in this substudy is not reported, 44 percent in the overall study used tobacco or alcohol.[37]

Screening by general dentists. Two studies conducted in London assessed screening by general dentists.[38,39] In the larger, good-quality study, subjects age 40 years or older were recruited from outpatients at a dental hospital or their relatives and from an inner-city medical practice.[39] All subjects drank alcohol and 38 percent smoked tobacco. Screening examinations took place at the dental hospital or the medical practice. Subjects were examined by a general dental practitioner, a community dental officer, or a junior hospital dentist. Screening dentists were educated as to what constituted a positive or negative screen, but were given no special training. Each subject was examined independently by a dental specialist during the same visit.

Study dentists screened 2,027 subjects. The screening dentist identified 60 lesions, 40 of which were confirmed as being abnormal by the specialist dentist. Using the specialty dentist's examination as the reference standard, the screening dentist's examination showed a sensitivity of 74 percent, specificity of 99 percent, positive predictive value of 67 percent, and negative predictive value of 99 percent.

In the smaller, fair-quality study, a commercial company's staff members who were age 40 years or older were invited for screening.[38] Screening was conducted at the on-site company dental practice by two general dentists who had not received any special training. During the same visit, each subject was subsequently examined independently by a specialist in oral medicine who was not aware of the screening dentist's findings.

Among 553 eligible staff at headquarters, 292 (53%) were screened. Seventeen staff from a separate company work site were also included in the analysis, providing a total of 309 subjects. The proportion using tobacco or alcohol was not reported. The screening dentist identified 14 abnormal lesions, 12 of which were confirmed as being abnormal by the oral medicine specialist. Using the oral medicine specialist's examination as a reference standard, the examination by the screening dentist showed a sensitivity of 71 percent, specificity of 99 percent, positive predictive value of 86 percent, and negative predictive value of 98 percent. This study was rated fair quality because of low participation rates and contamination from the second work site.

Mouth self-examination. Two fair-quality studies assessed mouth self-examination for oral cancer screening.[44,45] One study was conducted among 48,080 subjects older than age 10 years who were living in two administrative units of the Trivandrum District in Kerala, India.[44] Full-color brochures were distributed to all households in the study area. The brochures explained oral cancer and its risk factors, described mouth self-examination with words and pictures, and told people to report to the oral cancer screening clinic within 3 to 4 weeks if they found any of the abnormal lesions described.

Four weeks after the brochures were distributed, health workers with 1 month of training in oral cancer screening conducted a visual oral examination on 34,766 subjects (72% of those eligible for the study). Of these, 18 percent (33% of men and 3% of women) smoked cigarettes, chewed betel quid, or drank alcohol. Eighty-seven percent of subjects had actually performed the mouth self-examination and 54 subjects found lesions. Health workers confirmed 39 of these lesions as being abnormal. Only eight (21%) of the subjects with confirmed abnormal lesions presented for followup at the screening clinic. The health workers identified another 180 abnormal lesions that had not been found by self-examination. Using the health worker's examination as the reference standard, the mouth self-examination showed a sensitivity of 18 percent, specificity of 99.9 percent, positive predictive value of 72 percent, and negative predictive value of 99 percent. We rated this study as fair quality because it was unclear whether the health workers were aware of the screening results when performing their examinations.

The other study of self-examination recruited subjects who smoked and were age 45 years or older. A general practitioner in London identified 243 potential subjects, but only 53 (22%) participated in the screening exercise.[45] First, a dentist in an oral health services research department conducted an oral screening examination. Next, subjects were given a leaflet with text and pictures describing an oral self-examination. Then, the subjects conducted their own self-examinations with the dentist still in the room but not assisting. Among the 53 subjects, 23 found a lesion. The dentist's examination confirmed four of these lesions as being abnormal. However, the dentist's examination identified eight additional abnormal lesions. Using the dentist's examination as the reference standard, mouth self-examination showed a sensitivity of 33 percent, specificity of 54 percent, positive predictive value of 17 percent, and negative predictive value of 73 percent. We rated this study as fair quality because the dentist conducted an examination first (essentially teaching the subjects) and stayed in the room while subjects conducted their self-examination (influencing the self-examination), it included a small sample size, and the study's participation rate was low.

Toluidine blue. One fair-quality study evaluated toluidine blue for screening.[46] As part of a mass community screening program, 7,975 subjects living in Keelung County, Taiwan, who smoked cigarettes or chewed betel quid were screened for oral cancer. Subjects were randomized to gargle with toluidine blue solution or with placebo dye solution before the screening examination. Subjects were then examined by one of six dentists who had at last 3 years of practice experience and additional training. The patient was referred for biopsy if a dentist found an abnormal lesion. The investigators followed up with the subjects longitudinally through national cancer and death registries for incidence of oral cancer, survival status, and death during 4 to 5 years after the screening examination.

Among the 4,080 subjects who gargled with toluidine blue, the dentist identified 389 participants (9.5%) with suspicious lesions. Among the 3,895 who gargled with placebo dye, the dentist identified 322 (8.3%) with suspicious lesions (p=0.047). Patients with suspicious lesions detected by screening were referred for biopsy; 86 percent of patients referred to biopsy (82.3% who gargled with toluidine blue and 91.0% who gargled with placebo dye) complied with this recommendation. However, there was no significant difference in the RR for potentially malignant or malignant lesions based on the biopsy results: 187 potentially malignant or malignant lesions were identified among those who gargled with toluidine blue (4.6%), while 170 potentially malignant or malignant lesions were identified among those who gargled with placebo dye (4.4%; RR, 1.05 [95% CI, 0.75 to 1.41]).

Use of toluidine blue did not significantly improve identification of less advanced lesions. The malignant transformation rate from potentially malignant lesions to oral cancer was 129 per 100,000 person-years among those who gargled with toluidine blue versus 420 per 100,000 person-years among those who gargled with placebo dye (RR, 0.31 [95% CI, 0.03 to 2.94]). The annual incidence rate of oral cancer was 28.0 per 100,000 person-years among those who gargled with toluidine blue versus 35.4 per 100,000 person-years among those who gargled with placebo dye (RR, 0.79 [95% CI, 0.24 to 1.23]). We rated this study as fair quality despite its large size and randomized, double-blind design because it had a differential compliance with followup for diagnostic biopsy that could have impacted the findings and a limited spectrum of patients.

Chapter 4. Discussion

Subjects in a high-prevalence population who were screened for oral cancer had no significant difference in incidence or mortality rates from oral cancer compared with subjects who were not screened. Screened patients, however, had oral cancer diagnosed at lower stages, with greater 5-year survival. This may simply reflect lead- or length-time bias. Within the subset of participants who were at high risk for oral cancer because of using tobacco or alcohol, screened subjects had a lower mortality rate from oral cancer. This evidence is suggestive, since it came from a subgroup analysis in a single study that was not based on rigorous subgroup methods.[47,48] We found no evidence on screening for oral cancer in the general or a selected high-risk U.S. population. The most applicable evidence came from studies in the United Kingdom of dental practices (two studies[38,39]) and self-examination (one study[45]).

Study designs and test performance characteristics for the oral screening examination varied widely, making it difficult to synthesize evidence and draw conclusions about the evidence as a whole. All studies were hampered by an imperfect reference standard of repeated screening by a presumed more expert examiner and by combining the detection of potentially malignant lesions with cancers. Thus, for screening approaches that appear promising and potentially applicable to the U.S. health care setting, longitudinal followup for impact on cancers would be necessary.

Although potentially confounded by population risk or other factors, it appeared that advanced health workers or dentists conducted the most accurate examinations. Among older adults (age 40 years or older) at somewhat increased risk due to alcohol and tobacco use, dental examinations were 71 to 77 percent sensitive, with positive predictive values of 67 to 86 percent and high specificity (98% to 99%). However, few lesions were detected and clear determination of high-risk status was not reported. In contrast to expert or trained screening examinations, self-examinations in India and London were not sensitive. Adding toluidine blue to the screening examination did not significantly improve the identification of premalignant or malignant lesions, nor impact the incidence of oral cancer, and we found no acceptable evidence for other adjunctive devices.

Other Systematic Reviews

We identified two systematic reviews that addressed KQ 1.[5,29] The only evidence these reviews included was from the same Trivandrum trial described above. These reviews did not identify any additional studies meeting our inclusion criteria. Both reviews concluded that there was insufficient evidence for or against using visual inspection and palpation to screen for oral cancer in the general population. These reviews, however, suggested that the screening examination might decrease mortality from oral cancer among people who use tobacco or alcohol.

Four systematic reviews addressed KQ 2.[5,28,29,42] These systematic reviews did not identify any additional studies meeting our inclusion criteria. No systematic review found evidence to support using any adjunctive method for screening.[5,28,29,42] One of the systematic reviews assessed the test characteristics of the oral screening examination by conducting a meta-analysis of eight primary studies.[42] The weighted pooled value for sensitivity was 0.848 (95% CI, 0.730 to 0.919) and specificity was 0.965 (95% CI, 0.930 to 0.982). That review included primary studies that did not meet our inclusion criteria, including two large studies with artificially high sensitivity and low specificity.[49,50] These studies skewed the pooled results in the meta-analysis, making the test performance characteristics much different than those found in most of the primary studies in our review.

Cost-Effectiveness

Three cost-effectiveness studies found that screening high-risk individuals (variously defined, but including several of these: age older than 40 years, male sex, regular use of tobacco and alcohol) for oral cancer may be cost-effective. One study analyzed the cost-effectiveness of screening based on the experience in the Trivandrum trial (India).[51] In that setting, the incremental cost was U.S. $835 per year of life saved when screening everyone and U.S. $156 per year of life saved when screening only individuals at high risk due to using tobacco or alcohol. A second health technology assessment simulated various screening approaches in primary medical or dental care in the United Kingdom using a decision-analysis model; only opportunistic screening of high-risk individuals by general dentists (and perhaps medical doctors) was potentially cost-effective, but only if treatment was presumed to prevent precancerous disease progression and malignant transformation.[52] Little evidence was located to support this assumption. A third Markov decision-analysis model set in the United States suggested that annual screening of men older than age 40 years who smoked or drank alcohol using trained community health workers and a community outreach program might prove cost-effective compared with no screening; however, these results were primarily intended to inform future research for screening program development.[53]

Limitations

Screening for a PMD or oral cancer is based on the premise that treating the lesion will prevent its progression to oral cancer or to higher stages of oral cancer, thus decreasing morbidity and mortality.[54] This requires that subjects who screen positive present for followup to receive definitive diagnosis and treatment. In the RCT,[37] followup was 63 percent; in studies of test performance, followup ranged from 21[44] to 86 percent.[46] Low percentages of patients presenting for followup would diminish the effect of screening on clinical outcomes. The treatment interventions available for subjects with true-positive lesions identified in the RCT were not described.[37]

The screening methods tested in several of these studies may not be generalizable to the U.S. population, where the health care model does not incorporate home visits or health workers. Also, all evidence comes from Taiwan, India, and the United Kingdom, and two of these countries have markedly different oral cancer incidence and mortality rates from the United States (**Table 2**).

Test performance suggested by screening studies conducted in countries other than the United Kingdom will likely misrepresent test performance in the United States, a country with a lower prevalence of disease.[54] The prevalence of leukoplakia is 1.9 percent in the United States, for example, but 26.9 percent in Taiwan.[8] Also, although a high-risk subgroup of alcohol and tobacco users showed a mortality benefit in the Indian RCT, these results were based on post-hoc subgroup analysis and could also reflect numerous other differences in behavioral risk factors between the United States and Asia.

Results among selected higher-risk groups in populations similar to the United States may not apply when high-risk groups are not similarly characterized as to risk factors. Dental examination studies in the United Kingdom did not clearly specify high-risk status with regard to smoking and alcohol use. Thus, while some results may apply to members of the U.S. population who use tobacco or alcohol, this possibility would need to be confirmed using clear, reproducible definitions of high risk and screening approaches compatible with the U.S. health care system.

None of the studies in our review reported on harms from the screening test itself or from false-positive or false-negative test results. Screening using visual inspection and palpation should be low risk. However, any time devoted to it would reduce opportunity for other interventions that might have greater impact on health outcomes. Positive predictive values for the oral screening examination ranged from 17[45] to 87 percent,[38,40] with better results confined to more expert examiners. The wide range of results indicates the potential for many false-positive screening results. These might incur unnecessary patient anxiety, time and cost of followup visits, and biopsy-related harms. Except for mouth self-examination, which was generally unsupported by available evidence, negative predictive values were 98 to 99.3 percent, indicating few false-negative screening examinations.

The designs of the primary studies related to KQ 2 had considerable heterogeneity, as they were conducted using different screening examinations by people with different levels of training, in different clinical settings, in different countries, and using study populations with various ages and risk factors. All studies of test performance used examinations conducted by a clinician more highly trained than the screener as the reference standard. The outcomes of the primary studies also showed considerable heterogeneity, with wide variation in test performance characteristics. In addition to the range of positive predictive values described above, sensitivity ranged from 18[44] to 94.3 percent.[40] Sensitivity is important, as it reflects the screening test's ability to identify most people who have the disease.[54,55]

Current U.S. Recommendations

The American Dental Association does not recommend screening for oral cancer, but does suggest that clinicians remain alert for signs of potentially malignant lesions or early-stage cancers in all patients while performing routine visual and tactile examinations.[29] However, that suggestion has the lowest rating for strength of recommendation. The HealthPartners Dental Group and Clinics states "visual examination of the oral soft tissues, extraoral head and neck tissues and palpation of head and neck lymph nodes is considered the standard of care as part of a complete dental examination," but does not describe the strength of the recommendation.[56]

Future Research Needs

Screenings conducted by advanced health workers in the Trivandrum District achieved good sensitivity and positive predictive value. Similar advanced health workers in the U.S. health care model might be dental hygienists. Screening by general dentists in the United Kingdom was moderately sensitive as well for detecting PMDs and oral cancers. Longitudinal followup of applicable screening studies would clarify the screening impact on cancers. Targeted screening in those subjects who are at high risk for oral cancer due to patterns of tobacco or alcohol use could maximize screening's efficiency as well as effect on mortality from oral cancer. A clear definition of high-risk patients, with examination of the accuracy and impact of screening among such high-risk patients by dental hygienists, dentists, or other trained experts in U.S. settings would clarify if there is any role for screening in any high-risk group in the United States. If HPV becomes a more prominent risk factor for oral cancer, the benefits of screening and selection of high-risk populations could change.

Conclusion

Evidence for the effect of oral screening on morbidity and mortality from oral cancer comes from a single, large RCT (n=191,873) conducted in a population with high disease prevalence who were screened by advanced health workers during home visits. Screened subjects had no significant difference in incidence or mortality rates from oral cancer compared with subjects who were not screened. Screened subjects, however, had oral cancer diagnosed at lower stages and with greater 5-year survival. Exploratory analyses in the subgroup who used tobacco or alcohol (n=84,600) showed screened subjects had a lower mortality rate from oral cancer than subjects who were not screened. Evidence for the performance characteristics of the screening examination came from seven primary studies (n=86,513) conducted primarily in high-prevalence settings. The studies had considerable heterogeneity in design and showed wide variation in performance characteristics: sensitivity for oral cancer or PMD ranged from 18 to 94.3 percent and specificity from 54 to 99.9 percent, the positive predictive value ranged from 17 to 86.6 percent, and the negative predictive value from 73 to 99.3 percent. Among older adults (age 40 years or older) in the United Kingdom at somewhat increased risk due to alcohol and tobacco use, dental examinations were 71 to 77 percent sensitive, with positive predictive values of 67 to 86 percent and high specificity (98% to 99%). However, test performance reflected detection of potentially malignant lesions as well as actual cancers, the reference standard was flawed, few lesions were detected, and clear determination of high-risk status was not reported. In contrast to expert or trained screening examinations, self-examinations in India and London were clearly insensitive. We found no evidence on screening the general or a selected high-risk U.S. population for oral cancer. No study reported on harms from the screening test or from false-positive or false-negative test results. Adjunctive toluidine blue dye to enhance the screening examination did not significantly improve detection of lesions nor reduce oral cancer incidence compared with a placebo-dye screening examination. No study evaluating other adjuncts (chemiluminescent lighting, autofluorescent lighting, or brush cytopathology) met our inclusion criteria.

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Figure 1. Incidence[13] and Mortality[14] Rates of Cancer of the Oral Cavity and Pharynx in the United States by Age, SEER 2008

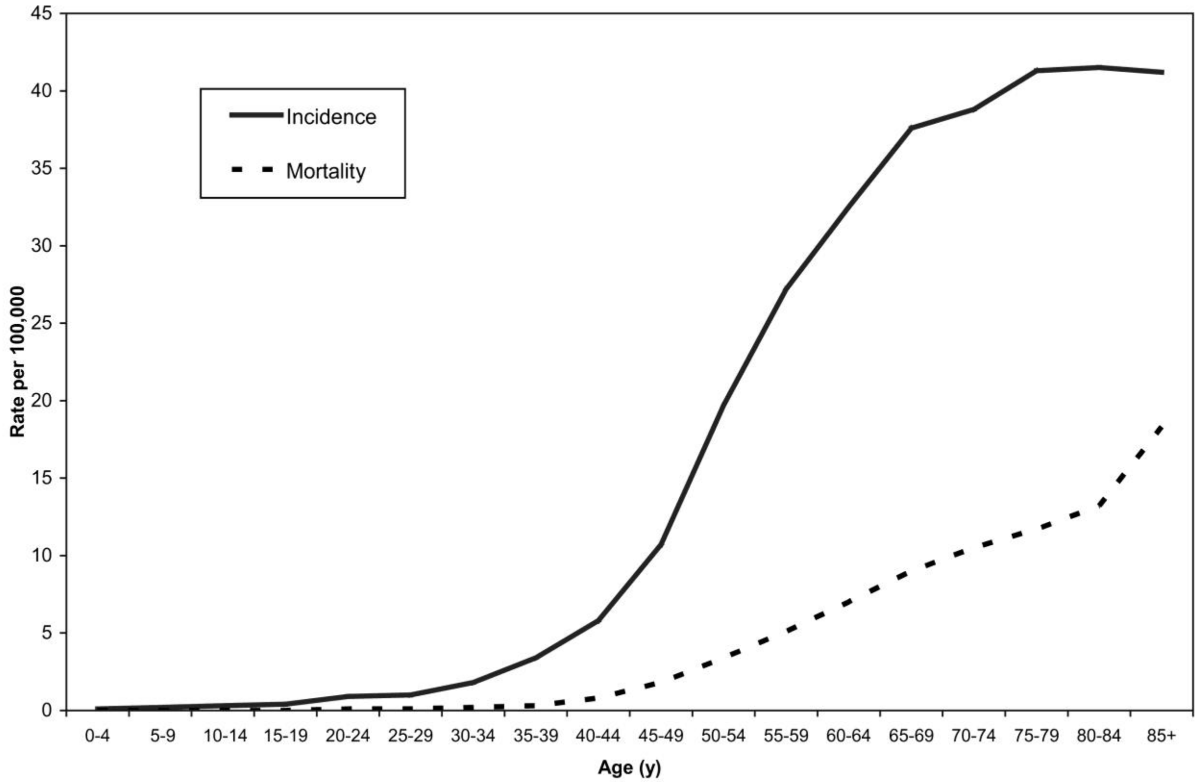

Figure 2. Literature Flow Diagram

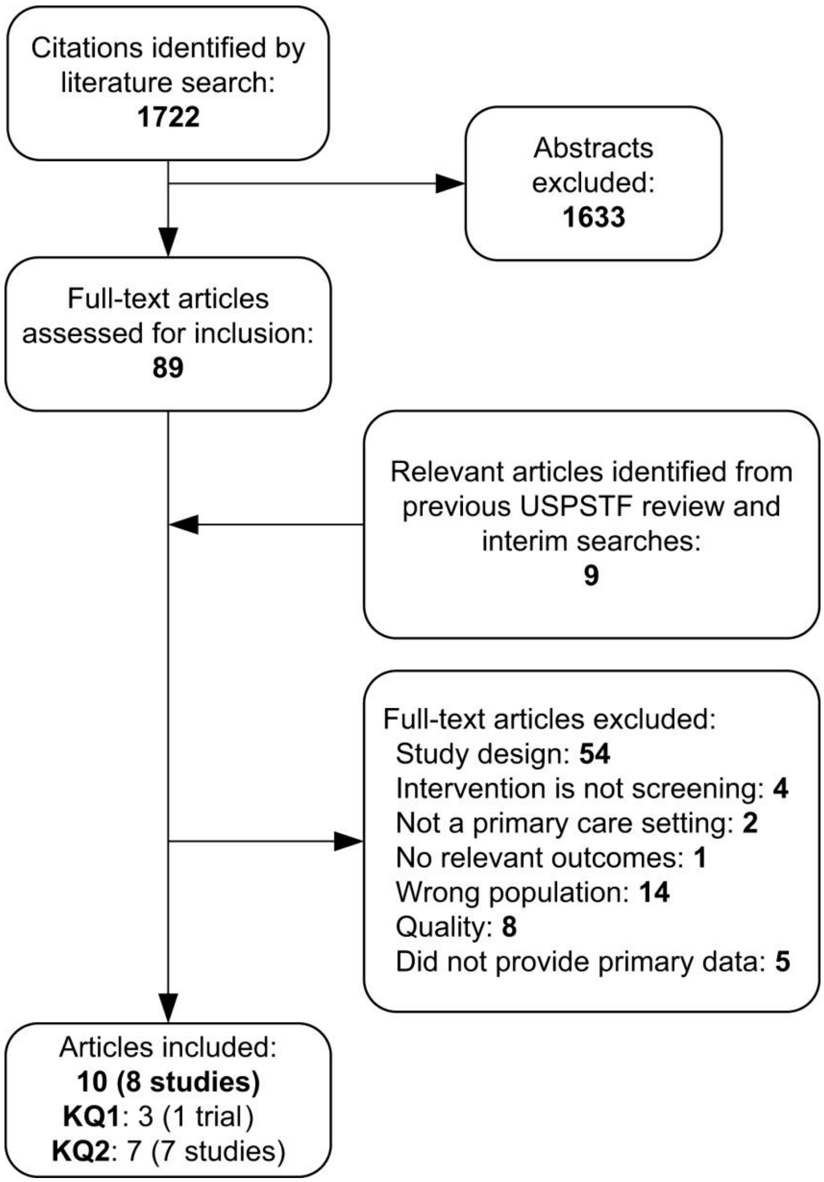

Table 1. Evidence for Key Question 2: Studies of Performance Characteristics of the Oral Cancer Screening Examination

Author, year Country	Participants, behaviors, and setting*	Criteria for positive screening test	Identity and training of screeners	Reference standard	Results	Comments	Quality rating
Examination by health workers							
Mehta et al, 1986[41] India	1,921 tobacco users age ≥35 years residing in Trivandrum District, India; proportion using alcohol NR Subjects' homes	Presence of nodular leukoplakia, submucous fibrosis, ulcers, or growths suggestive of oral cancer	Basic health workers (high school + 1 year) who received 2 or 5 days of training on how to perform oral exams and classify lesions	Dentist's exam 6 months after screening exam	Sensitivity=59% (16/27) Specificity=98% (1,859/1,894) PPV=31% (16/51) NPV=99% (1,859/1,870)	Selected for reference exam from 39,331 who were screened. Unclear if dentists were aware of screening results when performing their exams. Study conducted in a high-risk population.	Fair
Mathew et al, 1997[40] India	2,069 persons age 35 to 64 years residing in Trivandrum District, India; proportion using tobacco or alcohol NR Subjects' homes	Presence of homogeneous leukoplakia, ulcerated leukoplakia, verrucous leukoplakia, erythroplakia, nodular leukoplakia, submucous fibrosis, or growths suggestive of oral cancer	Advanced health workers (university graduates) who received 6 weeks of training on oral visual inspection and detection of lesions	Physician's exam 1 to 6 months after screening exam	Sensitivity=94.3% (200/212) Specificity=98.3% (1,826/1,857) PPV=86.6% (200/231) NPV=99.3% (1,826/1,838)	Selected for re-exam from about 9,000 screened based on population density. Substudy of RCT among general population.[37]	Good
Examination by general dentists							
Jullien et al, 1995[39] United Kingdom	2,027 patients and relatives age ≥40 years of a general dental or medical practice in London; 38% smoked, all drank alcohol Dental hospital or medical practice	White patch, red patch, or ulcer of >2 weeks duration or presence of specific lesions: lichen planus, lupus erythematosus, submucous fibrosis, or actinic keratosis	General dental practitioner, community dental officer, or junior hospital dentist	Dental specialist at the same visit	Sensitivity=74% (40/54) Specificity=99% (1,953/1,973) PPV=67% (40/60) NPV=99% (1,953/1,967)	Participation rate NR. Dental clinic patients might be more likely to have oral lesions than general population, and screeners may perform more thorough exams.	Good
Downer et al, 1995[38] United Kingdom	309 persons age ≥40 years employed by a commercial company in London; proportion using tobacco or alcohol NR Company dental practice	White patch, red patch, or ulcer of >2 weeks duration	General dentists with no special training	Oral medicine specialist at same visit	Sensitivity=71% (12/17) Specificity=99% (290/292) PPV=86% (12/14) NPV=98% (290/295)	53% of those eligible participated; sample enriched from second work site.	Fair

Table 1. Evidence for Key Question 2: Studies of Performance Characteristics of the Oral Cancer Screening Examination

Author, year Country	Participants, behaviors, and setting*	Criteria for positive screening test	Identity and training of screeners	Reference standard	Results	Comments	Quality rating
Mouth self-examination							
Elango et al, 2011[44] India	34,766 persons age >10 years residing in Trivandrum District, India (47% ≥40 years); 33% of men and 3% of women used tobacco, betel quid, or alcohol (17.6% total) Subjects' homes	Presence of white patch, red patch, nonhealing ulcer, difficulty opening mouth, other oral symptoms	Subjects performing mouth self-exam as described in brochure	Health worker with 1 month of training on oral cancer conducted exam 4 weeks after screening exam	Sensitivity=18% (39/219) Specificity=99.9% (34,532/34,547) PPV=72% (39/54) NPV=99% (34,532/34,712)	72% of those eligible were examined by health worker. 87% performed mouth self-exam. Only 21% (8/39) with potentially malignant lesions confirmed by health worker followed up at screening clinic	Fair
Scott et al, 2010[45] United Kingdom	53 persons age ≥45 years who smoked (as identified by a general practitioner) residing in London; proportion using alcohol NR Research department	Presence of ulcer, white patch, red patch, lump, or swelling	Subjects performing mouth self-exam as described in a leaflet, after a screening exam by a dentist	Dentist, at same visit	Sensitivity=33% (4/12) Specificity=54% (22/41) PPV=17% (4/23) NPV=73% (22//30)	22% of those invited participated. Mouth self-exam conducted in research department after dentist's exam with dentist in the room. Small sample size. Study conducted in a high-risk population.	Fair
Toluidine blue							
Su et al, 2010[46] Taiwan	7,975 persons age ≥15 years (61% ≥40 years) who smoked cigarettes or chewed betel quid residing in Keelung, Taiwan; proportion using alcohol NR Community setting	Presence of any visible lesion including submucous fibrosis, leukoplakia, erythroplakia, lichen planus, ulcer, hyperkeratosis, candidiasis	Dentists with at least 3 years of practice and additional training; exam with or without toluidine blue	Incidence of oral cancer from National Cancer Registry during 4 to 5 years of followup	Malignant transformation rate in toluidine blue group: 129 per 100,000 person-years Malignant transformation rate in placebo dye group: 420 per 100,000 person-years Relative malignant transformation rate, toluidine blue vs. placebo dye: 0.31 (95% CI, 0.03 to 2.94) Annual incidence of oral cancer in toluidine blue group: 28.0 per 100,000 person-years Annual incidence in placebo dye group: 35.4 per 100,000 person-years Relative incidence of oral cancer, toluidine blue vs. placebo dye: 0.79 (95% CI, 0.24 to 1.23)	78% of those eligible participated. Study conducted in a high-risk population.	Fair

*Participants who had reference standard.

Abbreviations: NR: not reported; NPV: negative predictive value; PPV: positive predictive value; RCT: randomized, controlled trial

Table 2. National Incidence and Mortality Rates of Lip and Oral Cavity Cancer Only, IARC 2008[19]

Country	Study site	Incidence rate*	Mortality rate*
Taiwan	Keelung County	16.1	6.0
India	Trivandrum District	7.5	5.2
United States	---	5.0	0.7
United Kingdom	London	3.6	1.0

*Age-adjusted rates per 100,000 persons. Unlike SEER data, the International Agency for Research on Cancer (IARC) reports data for the lip and oral cavity without including the pharynx.

Appendix A. Literature Search Terms

Terms pertaining to oral cancer:
mouth neoplasms/
gingival neoplasms/
leukoplakia, oral/
lip neoplasms/
palatal neoplasms/
salivary gland neoplasms/
parotid neoplasms/
sublingual gland neoplasms/
submandibular gland neoplasms/
tongue neoplasms/
pharyngeal neoplasms/
hypopharyngeal neoplasms/
nasopharyngeal neoplasms/
oropharyngeal neoplasms/
tonsillar neoplasms/
((oral or mouth or lip$ or tongue$ or gingiv$ or oropharyn$ or pharyn$ or palate or cheek$) adj5 (cancer$ or carcinoma$ or neoplas$ or tumor$ or tumour$ or dysplasia$ or malignan$)).ti,ab.

Terms pertaining to screening:
Mass Screening/
"early detection of cancer"/
early diagnosis/
screen$.ti,ab.
(early adj3 (diagnos$ or detect$)).ti,ab.

Terms pertaining to diagnostic accuracy:
"Sensitivity and Specificity"/
"Predictive Value of Tests"/
ROC Curve/
False Negative Reactions/
False Positive Reactions/
Diagnostic Errors/
"Reproducibility of Results"/
Reference Values/
Reference Standards/
specificit$ti,ab.
sensitiv$.ti,ab.
predictive value.ti,ab.
accurac$.ti,ab.
miss rate$.ti,ab.
detection rate$.ti,ab.
diagnostic yield$.ti,ab.
likelihood ratio$.ti,ab.
diagnostic odds ratio$.ti,ab.
odds ratio/ and di.fs.

Appendix B. Excluded Studies

1. Chip developed to diagnose oral cancer in ten minutes. Br Dent J 2010 Aug 28;209(4):155. PMID: 20798709. **Not one of the specified study designs.**
2. High-tech oral cancer detection. Less invasive, less painful microchip technology could identify mouth cancers in the very early stages. Duke Med Health News 2010 Nov;16(11):4-5. PMID: 21186497. **Not one of the specified study designs.**
3. Screening for oral cancer. Med Lett Drugs Ther 2009 Feb 23;51(1306):15-16. PMID: 19229163. **Not one of the specified study designs.**
4. Ahmed HG, Ebnoof SO, Hussein MO, et al. Oral epithelial atypical changes in apparently healthy oral mucosa exposed to smoking, alcohol, peppers and hot meals, using the AgNOR and Papanicolaou staining techniques. Diagn Cytopathol 2010 Jul;38(7):489-95. PMID: 19894260. **No relevant outcomes.**
5. Al-Tarawneh SK, Border MB, Dibble CF, et al. Defining salivary biomarkers using mass spectrometry-based proteomics: a systematic review. OMICS 2011 Jun;15(6):353-61. PMID: 21568728. **Intervention does not involve screening.**
6. Balevi B. Assessing the usefulness of three adjunctive diagnostic devices for oral cancer screening: a probabilistic approach. Community Dent Oral Epidemiol 2011 Apr;39(2):171-76. PMID: 21029147. **Not one of the specified study designs.**
7. Baykul T, Yilmaz HH, Aydin U, et al. Early diagnosis of oral cancer. J Int Med Res 2010 May;38(3):737-49. PMID: 20819411. **Not one of the specified study designs.**
8. Bhalang K, Suesuwan A, Dhanuthai K, et al. The application of acetic acid in the detection of oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008 Sep;106(3):371-76. PMID: 18547833. **Wrong population.**
9. Bhoopathi V, Mascarenhas AK. Effectiveness of oral surgeons compared with OralCDx brush biopsy in diagnosing oral dysplastic lesions. J Oral Maxillofac Surg 2011 Feb;69(2):428-31. PMID: 21122966. **Wrong population.**
10. Bocking A, Sproll C, Stocklein N, et al. Role of brush biopsy and DNA cytometry for prevention, diagnosis, therapy, and followup care of oral cancer. J Oncol 2011;2011:875959. PMID: 21209723. **Not one of the specified study designs.**
11. Brocklehurst P, Kujan O, Glenny AM, et al. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev 2010;11:CD004150. PMID: 21069680. **Did not provide primary data.**
12. Brocklehurst PR, Baker SR, Speight PM. Oral cancer screening: what have we learnt and what is there still to achieve? Future Oncol 2010 Feb;6(2):299-304. PMID: 20146588. **Not one of the specified study designs.**
13. Brocklehurst PR, Baker SR, Speight PM. Primary care clinicians and the detection and referral of potentially malignant disorders in the mouth: a summary of the current evidence. Prim Dent Care 2010 Apr;17(2):65-71. PMID: 20353654. **Not one of the specified study designs.**
14. Chaturvedi P, Majumder SK, Krishna H, et al. Fluorescence spectroscopy for noninvasive early diagnosis of oral mucosal malignant and potentially malignant lesions. J Canc Res Ther 2010 Oct;6(4):497-502. PMID: 21358088. **Not an appropriate setting.**
15. Chen CH, Chen RJ. Prevalence of telomerase activity in human cancer. J Formos Med Assoc 2011 May;110(5):275-89. PMID: 21621148. **Not one of the specified study designs.**
16. Choi CW, Lee MC, Ng WT, et al. An analysis of the efficacy of serial screening for familial nasopharyngeal carcinoma based on Markov chain models. Fam Cancer 2011 Mar;10(1):133-39. PMID: 21052850. **Not one of the specified study designs.**
17. DeCoro M, Wilder-Smith P. Potential of optical coherence tomography for early diagnosis of oral malignancies. Expert Rev Anticancer Ther 2010 Mar;10(3):321-29. PMID: 20214513. **Not one of the specified study designs.**
18. Delavarian Z, Mohtasham N, Mosannen-Mozafari P, et al. Evaluation of the diagnostic value of a Modified Liquid-Based Cytology using OralCDx Brush in early detection of oral potentially malignant lesions and oral cancer. Med Oral Patol Oral Cir Bucal 2010;15(5):e671-e676. PMID: 20383114. **Wrong population.**
19. Demko CA, Sawyer D, Slivka M, et al. Prevalence of oral lesions in the dental office. Gen Dent 2009 Sep;57(5):504-09. PMID: 19903642. **Quality issues.**
20. Downer MC, Moles DR, Palmer S, et al. A systematic review of test performance in screening for oral cancer and precancer. Oral Oncol 2004 Mar;40(3):264-73. PMID: 14747057. **Did not provide primary data.**

21. Epstein JB, Silverman S Jr, Epstein JD, et al. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. Oral Oncol 2008 Jun;44(6):538-44. PMID: 17996486. **Wrong population.**
22. Epstein JB, Villines D, Drahos G, et al. Oral lesions in patients participating in an oral examination screening week at an urban dental school. J Am Dent Assoc 2008 Oct;139(10):1338-44. PMID: 18832269. **Not one of the specified study designs.**
23. Epstein JB, Gorsky M, Cabay RJ, et al. Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma: role of primary care physicians. Can Fam Physician 2008 Jun;54(6):870-75. PMID: 18556495. **Not one of the specified study designs.**
24. Epstein JB, Guneri P. The adjunctive role of toluidine blue in detection of oral premalignant and malignant lesions. Curr Opin Otolaryngol Head Neck Surg 2009 Apr;17(2):79-87. PMID: 19374030. **Quality issues.**
25. Fedele S. Diagnostic aids in the screening of oral cancer. Head Neck Oncol 2009;1:5. PMID: 19284694. **Not one of the specified study designs.**
26. Guneri P, Epstein JB, Kaya A, et al. The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions. Int J Oral Maxillofac Surg 2011 Feb;40(2):155-61. PMID: 21112183. **Wrong population.**
27. Gurenlian JR. Diagnostic devices for detecting oral cancer. J Dent Hyg 2009;83(4):177-78. PMID: 19909635. **Not one of the specified study designs.**
28. Hakama M, Coleman MP, Alexe DM, et al. Cancer screening: evidence and practice in Europe 2008. Eur J Cancer 2008 Jul;44(10):1404-13. PMID: 18343653. **Not one of the specified study designs.**
29. Haxel BR, Goetz M, Kiesslich R, et al. Confocal endomicroscopy: a novel application for imaging of oral and oropharyngeal mucosa in human. Eur Arch Otorhinolaryngol 2010 Mar;267(3):443-48. PMID: 19590883. **Quality issues.**
30. Hoffmann RR, Yurgel LS, Campos MM. Endothelins and their receptors as biological markers for oral cancer. Oral Oncol 2010 Sep;46(9):644-47. PMID: 20656542. **Not one of the specified study designs.**
31. Huber MA. Assessment of the VELscope as an adjunctive examination tool. Tex Dent J 2009 Jun;126(6):528-35. PMID: 19639920. **Quality issues.**
32. Huff K, Stark PC, Solomon LW. Sensitivity of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice. Gen Dent 2009 Jan;57(1):34-38. PMID: 19146141. **Quality issues.**
33. Huff KD. Cancer screening. J Am Dent Assoc 2008;139(10):1304. PMID: 18832263. **Not one of the specified study designs.**
34. Huff KD. Photography: an integral component of oral cancer screening. Dent Today 2009 Sep;28(9):100. PMID: 19771969. **Not one of the specified study designs.**
35. Kanatas A, McCaul JA. Re: use of Lugol's iodine in oral cancer diagnosis: an overview. Oral Oncol 2010 Nov;46(11):835. PMID: 20947412. **Not one of the specified study designs.**
36. Kao SY, Chu YW, Chen YW, et al. Detection and screening of oral cancer and pre-cancerous lesions. J Chin Med Assoc 2009 May;72(5):227-33. PMID: 19467945. **Not one of the specified study designs.**
37. Katz P, Hartl DM, Guerre A. Clinical ultrasound of the salivary glands. Otolaryngol Clin North Am 2009;42(6):973-1000. PMID: 19962004. **Not one of the specified study designs.**
38. Kelloff GJ, Sigman CC, Contag CH. Early detection of oral neoplasia: watching with new eyes. Cancer Prev Res 2009 May;2(5):405-08. PMID: 19401527. **Not one of the specified study designs.**
39. Kujan O, Glenny AM, Oliver RJ, et al. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev 2006;3:CD004150. PMID: 16856035. **Did not provide primary data.**
40. Le A, Messadi D, Epstein J, et al. Toward multimodality oral cancer diagnosis in the XXI century: Blending cutting edge imaging and genomic/proteomic definition of suspicious lesions. Bioinformation 2010;5(7):304-06. PMID: 21364840. **Not one of the specified study designs.**
41. Li S, Deng Y, Li X, et al. Diagnostic value of Epstein-Barr virus capsid antigen-IgA in nasopharyngeal carcinoma: a meta-analysis. Chin Med J (Engl) 2010 May 5;123(9):1201-05. PMID: 20529563. **Wrong population.**
42. Lingen MW, Kalmar JR, Karrison T, et al. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008 Jan;44(1):10-22. PMID: 17825602. **Not one of the specified study designs.**

43. Lingen MW, Pinto A, Mendes RA, et al. Genetics/epigenetics of oral premalignancy: current status and future research. Oral Dis 2011 Apr;17:Suppl-22. PMID: 21382136. **Intervention does not involve screening.**
44. Lopez-Jornet P, De la Mano-Espinosa T. The efficacy of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice: an update. Int J Dent Hyg 2011 May;9(2):97-100. PMID: 21356007. **Quality issues.**
45. McIntosh L, McCullough MJ, Farah CS. The assessment of diffused light illumination and acetic acid rinse (Microlux/DL) in the visualisation of oral mucosal lesions. Oral Oncol 2009 Dec;45(12):e227-e231. PMID: 19800285. **Wrong population.**
46. Mehrotra R, Singh M, Thomas S, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc 2010 Feb;141(2):151-56. PMID: 20123872. **Wrong population.**
47. Mehrotra R, Hullmann M, Smeets R, et al. Oral cytology revisited. J Oral Pathol Med 2009 Feb;38(2):161-66. PMID: 19213102. **Quality issues.**
48. Messadi DV, Wilder-Smith P, Wolinsky L. Improving oral cancer survival: the role of dental providers. CDA J 2009 Nov;37(11):789-98. PMID: 19998655. **Not one of the specified study designs.**
49. Moro A, Di NF, Boniello R, et al. Autofluorescence and early detection of mucosal lesions in patients at risk for oral cancer. J Craniofac Surg 2010 Nov;21(6):1899-903. PMID: 21119451. **Not one of the specified study designs.**
50. Murrah VA. Dentistry and the prevention, diagnosis, and treatment of oral cancer in North Carolina. N C Med J 2008 Jul;69(4):313-15. PMID: 18828326. **Not one of the specified study designs.**
51. Nagler RM. Saliva as a tool for oral cancer diagnosis and prognosis. Oral Oncol 2009 Dec;45(12):1006-10. PMID: 19828359. **Not one of the specified study designs.**
52. Naugler C. Practice tips. Brush biopsy sampling of oral lesions. Can Fam Physician 2008 Feb;54(2):194. PMID: 18272633. **Not one of the specified study designs.**
53. Navone R, Pentenero M, Gandolfo S. Liquid-based cytology in oral cavity squamous cell cancer. Curr Opin Otolaryngol Head Ne 2011 Apr;19(2):77-81. PMID: 21252668. **Not one of the specified study designs.**
54. Nieman LT, Kan CW, Gillenwater A, et al. Probing local tissue changes in the oral cavity for early detection of cancer using oblique polarized reflectance spectroscopy: a pilot clinical trial. J Biomed Opt 2008 Mar;13(2):024011-Apr. PMID: 18465974. **Wrong population.**
55. Palmer O, Grannum R. Oral cancer detection. Dent Clin North Am 2011 Jul;55(3):537-48. PMID: 21726688. **Not one of the specified study designs.**
56. Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc 2008;139(7):896-905. PMID: 18594075. **Did not provide primary data.**
57. Perrone F, Gloghini A, Cortelazzi B, et al. Isolating p16-positive/HPV-negative oropharyngeal cancer: an effort worth making. Am J Surg Pathol 2011;35(5):774-77. PMID: 21436677. **Wrong population.**
58. Petruzzi M, Lucchese A, Baldoni E, et al. Use of Lugol's iodine in oral cancer diagnosis: an overview. Oral Oncol 2010 Nov;46(11):811-13. PMID: 20729139. **Intervention does not involve screening.**
59. Pfaffe T, Cooper-White J, Beyerlein P, et al. Diagnostic potential of saliva: current state and future applications. Clin Chem 2011 May;57(5):675-87. PMID: 21383043. **Not one of the specified study designs.**
60. Piazza C, Dessouky O, Peretti G, et al. Narrow-band imaging: a new tool for evaluation of head and neck squamous cell carcinomas. Review of the literature. Acta Otorhinolaryngol Ital 2008 Apr;28(2):49-54. PMID: 18669067. **Not one of the specified study designs.**
61. Rahman M, Chaturvedi P, Gillenwater AM, et al. Low-cost, multimodal, portable screening system for early detection of oral cancer. J Biomed Opt 2008 May;13(3):030502-Jun. PMID: 18601519. **Not one of the specified study designs.**
62. Rahman MS, Ingole N, Roblyer D, et al. Evaluation of a low-cost, portable imaging system for early detection of oral cancer. Head Neck Oncol 2010;2:10. PMID: 20409347. **Wrong population.**
63. Remmerbach TW, Meyer-Ebrecht D, Aach T, et al. Toward a multimodal cell analysis of brush biopsies for the early detection of oral cancer. Cancer Cytopathol 2009 Jun 25;117(3):228-35. PMID: 19373897. **Wrong population.**

64. Rethman MP, Carpenter W, Cohen EE, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc 2010 May;141(5):509-20. PMID: 20436098. **Did not provide primary data.**
65. Rhodus NL. Oral cancer and precancer: improving outcomes. Compend Contin Educ Dent 2009 Oct;30(8):486-88. PMID: 19824564. **Not one of the specified study designs.**
66. Richards D. Clinical recommendations for oral cancer screening. Evid Based Dent 2010;11(4):101-02. PMID: 21170006. **Not one of the specified study designs.**
67. Richards D. Does toluidine blue detect more oral cancer? Evid Based Dent 2010;11(4):104-05. PMID: 21170008. **Not one of the specified study designs.**
68. Richards D. Oral cancer screening programmes. Evid Based Dent 2010;11(4):103. PMID: 21170007. **Not one of the specified study designs.**
69. Richards D. Seek don't screen for oral cancer. Evid Based Dent 2010;11(4):98. PMID: 21170004. **Not one of the specified study designs.**
70. Richards D. Should we screen for oral cancer? Evid Based Dent 2009;10(4):98. PMID: 20023609. **Not one of the specified study designs.**
71. Scheer M, Neugebauer J, Derman A, et al. Autofluorescence imaging of potentially malignant mucosa lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011 May;111(5):568-77. PMID: 21429774. **Not an appropriate setting.**
72. Scully C, Bagan JV, Hopper C, et al. Oral cancer: current and future diagnostic techniques. Am J Dent 2008 Aug;21(4):199-209. PMID: 18795514. **Not one of the specified study designs.**
73. Seoane LJ, Diz DP. Diagnostic clinical aids in oral cancer. Oral Oncol 2010 Jun;46(6):418-22. PMID: 20371204. **Not one of the specified study designs.**
74. Shin D, Vigneswaran N, Gillenwater A, et al. Advances in fluorescence imaging techniques to detect oral cancer and its precursors. Future Oncol 2010 Jul;6(7):1143-54. PMID: 20624126. **Not one of the specified study designs.**
75. Slater LJ. Comment on "analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue". Oral Oncol 2009 Mar;45(3):296-98. PMID: 19147390. **Not one of the specified study designs.**
76. Sok JC, Grandis JR. Genetic screening for oral human papillomavirus infections and cancers of the head and neck. Clin Cancer Res 2008 Nov 1;14(21):6723-24. PMID: 18980962. **Not one of the specified study designs.**
77. Steele TO, Meyers A. Early detection of premalignant lesions and oral cancer. Otolaryngol Clin North Am 2010;44(1):221-29. PMID: 21093631. **Not one of the specified study designs.**
78. Trullenque-Eriksson A, Munoz-Corcuera M, Campo-Trapero J, et al. Analysis of new diagnostic methods in suspicious lesions of the oral mucosa. Med Oral Patol Oral Cir Bucal 2009 May;14(5):E210-E216. PMID: 19218907. **Quality issues.**
79. Wang TW, Lu HY, Lou PJ, et al. Application of highly sensitive, modified glass substrate-based immuno-PCR on the early detection of nasopharyngeal carcinoma. Biomaterials 2008 Nov;29(33):4447-54. PMID: 18752845. **Intervention does not involve screening.**
80. Warnakulasuriya S, Kashyap R, Dasanayake AP. Is workplace screening for potentially malignant oral disorders feasible in India? J Oral Pathol Med 2010 Oct;39(9):672-76. PMID: 20738753. **Not one of the specified study designs.**
81. Warnecke A, Averbeck T, Leinung M, et al. Contact endoscopy for the evaluation of the pharyngeal and laryngeal mucosa. Laryngoscope 2010 Feb;120(2):253-58. PMID: 19998420. **Wrong population.**
82. Willis RC. Identifying markers of premalignancy. J Proteome Res 2009 Jan;8(1):4. PMID: 19072116. **Not one of the specified study designs.**
83. Wu JY, Yi C, Chung HR, et al. Potential biomarkers in saliva for oral squamous cell carcinoma. Oral Oncol 2010 Apr;46(4):226-31. PMID: 20138569. **Not one of the specified study designs.**
84. Yao K, Takaki Y, Matsui T, et al. Clinical application of magnification endoscopy and narrow-band imaging in the upper gastrointestinal tract: new imaging techniques for detecting and characterizing gastrointestinal neoplasia. Gastrointest Endosc Clin N Am 2008 Jul;18(3):415-33. PMID: 18674694. **Not one of the specified study designs.**
85. Yokoyama A, Kumagai Y, Yokoyama T, et al. Health risk appraisal models for mass screening for esophageal and pharyngeal cancer: an endoscopic follow-up study of cancer-free Japanese men. Cancer Epidem Biomarker Prev 2009 Feb;18(2):651-55. PMID: 19190142. **Not one of the specified study designs.**

86. Zhou J, Cao J, Lu Z, et al. A 115-bp MethyLight assay for detection of p16 (CDKN2A) methylation as a diagnostic biomarker in human tissues. BMC Med Genet 2011;12:67. PMID: 21569495. **Wrong population.**
87. Zimmermann BG, Wong DT. Salivary mRNA targets for cancer diagnostics. Oral Oncol 2008 May;44(5):425-29. PMID: 18061522. **Not one of the specified study designs.**
88. Ziober BL, Mauk MG, Falls EM, et al. Lab-on-a-chip for oral cancer screening and diagnosis. Head Neck 2008 Jan;30(1):111-21. PMID: 17902150. **Not one of the specified study designs.**